Attempts to Prepare 1-Methyl 2-Methoxy-piperidine. The Hydrogenation of Certain Pyridine Derivatives

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DISSERTATION

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES
OF THE JOHNS HOPKINS UNIVERSITY IN CONFORMITY
WITH THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

BY

THOMAS BROOKS GRAVE

BALTIMORE

1923

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ACKNOWLEDGMENT

The author wishes to express his appreciation to Doctors Frazer, Reid, Patrick, Lovelace, and Thornton for their generous instruction and advice in the lecture room and laboratories of this Department, and to Doctors Abel, Lamson, and Macht for the privilege of attending their inspiring lectures in Pharmacology.

Special thanks are due Dr. Macht for suggesting the problem undertaken, and Dr. Reid for his sustained interest and guidance during its progress.

ATTEMPTS TO PREPARE 1-METHYL-2-METHOXYPIPERIDINE. THE HYDROGENATION OF CERTAIN PYRIDINE DERIVATIVES[1]

Introduction

This research was started with a view to synthesizing 1-methyl-2-methoxypiperidine and some of its homologs, in order to study their physiological action, but these have not yet been obtained. However, certain 2-substituted pyridines have been prepared and their transformation into the corresponding piperidines attempted; this paper deals with the results of these trials.

Four pyridine derivatives were used, successively, as starting points for the synthesis: 2-methoxypyridine, 2-chloropyridine, 2-aminopyridine, and 1-methyl-2-pyridone.

1. The most likely method appeared to consist in the hydrogenation and methylation of 2-methoxypyridine. Von Pechmann and Baltzer[2] first prepared this compound by the action of methyl iodide on the silver salt of 2-pyridone, and later von Pechmann[3] made it from 2-pyridone and

[1] The author also wishes to express his thanks to E .I. Du Pont de Nemours and Co., for the grant of a Du Pont Fellowship for the year 1922–23.

[2] Von Pechmann and Baltzer, *Ber.*, **24,** 3144 (1891).

[3] Von Pechmann, *Ber.*, **28,** 1624 (1895).

diazomethane. Although 2-pyridone is now far more readily accessible[4] than it was at the time of von Pechmann's work, it is nevertheless more convenient to prepare 2-methoxypyridine as follows. 1-Methyl-2-pyridone is converted by phosphorus pentachloride into 2-chloropyridine,[5] and this in turn by sodium methoxide in boiling methyl alcohol into 2-methoxypyridine. Sell[6] studied the action of this reagent on 2,3,4,5-tetrachloropyridine, but it has not previously been applied to 2-chloropyridine. The hydrogenation of 2-methoxypyridine has not been studied, except with a view to proving its constitution; von Pechmann and Baltzer[2] found that the drastic action of sodium amalgam splits the ring, giving ammonia. Hydrogenation was tried by three methods: (a) sodium in boiling ethyl alcohol,[7] (b) electrolytic reduction, using lead electrodes,[8] (c) catalytically, using hydrogen at 3.75 atmospheres' pressure; (1) in 40% acetic acid solution, with colloidal platinum.[9] These methods proved too energetic; in each case, the methoxyl group was split off, yielding methyl alcohol and piperidine.

(2) Hydrogenation in aqueous and in absolute methyl alcoholic hydrochloric acid, with platinum black, the amount of hydrogen being regulated.

The results show that the ring is hydrogenated before any methoxyl is split off, but methoxypiperidine is very susceptible to hydrogenation since it cannot be detected in the reduction product. Apparently, three-fourths of the methoxypyridine is converted into piperidine and methyl alcohol, and one-fourth remains unchanged. 2-Methoxy-methyl-pyridinium sulfate, too, is split into 1-methyl piperidine and methyl alcohol in absolute methyl alcoholic solution.

2. The regulated hydrogenation of 2-chloropyridine was next attempted. This compound has been reduced to piperidine and hydrogen chloride with sodium and alcohol by O. Fischer,[10] but it was thought possible that a high concentration of hydrogen chloride in alcohol might inhibit the splitting off of the chlorine until the ring should be completely hydrogenated. This was found not to be the case, however. After absorption of six atoms of hydrogen per molecule, piperidine and pyridine were found in the solution, showing that the first stage in the hydrogenation of chloropyridine is the formation of hydrogen chloride and pyridine.

3. The next starting point was 2-aminopyridine, the proposed steps

[4] Chichibabin, (Tschitschibabin) and Rjasanzew, *Chem. Centr.*, **1916**, II, 228.

[5] (a) O. Fischer, *Ber.*, **32**, 1298 (1899). (b) Fargher and Furness, *J. Chem. Soc.*, **107**, 690 (1915).

[6] Sell, *J. Chem. Soc.*, **101**, 1945 (1912).

[7] Ladenburg, *Ann.*, **247**, 51 (1888).

[8] Tafel, *Ber.*, **33**, 2209 (1900).

[9] Skita, *Ber.*, **45**, 3589 (1912).

[10] Ref. 5a, p. 1299.

in the synthesis being (1) hydrogenation to 2-aminopiperidine, (2) conversion to 2-piperidol by means of nitrous acid, (3) and (4) methylation of the hydroxyl and imino groups.

The formation of 2-aminopiperidine has been reported[11] but no proof of the structure is given and the compound is not recognized in the literature. Marckwald[12] reduced 2-aminopyridine with sodium and alcohol, and obtained, besides ammonia and piperidine, a higher-boiling base in such small quantity that it could not be analyzed. The results of the present investigation show that 2-aminopiperidine cannot be formed in an alkaline reduction medium, and that the possibility of its very existence is doubtful. The hydrogenation was carried out with three different forms of platinum as catalyst: (*a*) colloidal platinum, prepared by the method of Skita,[9] in aqueous solution containing excess hydrochloric acid, to prevent the splitting off of ammonia,[13] (*b*) platinum black, using excess hydrochloric acid, both in aqueous and in alcoholic solution; (*c*) freshly prepared *platinum oxide*,[14] in neutral aqueous solution.

Methods *a* and *b* gave quantitative yields of tetrahydro-aminopyridine; no amount of shaking at three atmospheres induced further addition of hydrogen. Method *c* gave more complete hydrogenation; it actually permitted the absorption of 8 atoms per molecule, with the formation of ammonia and piperidine. This indicated that there is a possibility of obtaining aminopiperidine, provided the reaction is stopped at the right point. The introduction of two atoms of hydrogen into the molecule of tetrahydro-aminopyridine was therefore attempted, but the result was four atoms for half the tetrahydro-aminopyridine used, the remainder being unchanged. Only ammonia, piperidine, and tetrahydro-aminopyridine could be isolated from the reduction product.

Tetrahydro-aminopyridine in the free state was found to be unstable; it is hydrolyzed by boiling water, and by cold concd. potassium hydroxide, to ammonia and 2-piperidone. An aqueous solution of the free base, prepared by decomposing the hydrochloride with silver oxide, has a strong ammoniacal odor in addition to the characteristic odor of piperidine; this odor is not due to free ammonia, because nitrogen, bubbled through the solution at room temperature for 12 hours, carries no ammonia with it. In dil. sulfuric acid the base was totally indifferent to nitrous acid, both at 0°, and at 100°, yet in the free state, it gave the Rimini test[15] for the primary amino group. A detailed study of the compound offered

[11] Levy, *Dissertation*, Erlangen, "Ueber die bei der Reduktion von Alkylen-cyaniden entstehenden Basen."

[12] Marckwald, *Ber.*, **27**, 1330 (1894).

[13] Skita, *Ber.*, **52**, 1520 (1919).

[14] Adams and Voorhees, *J. Am. Chem. Soc.*, **44**, 1397 (1922).

[15] Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, **1916**, vol. II, p. 35, Test 2.25.

interesting possibilities, but as it appeared to be useless as an intermediate in the synthesis of methoxypiperidine, it was not further investigated.

4. Finally, the reduction of 1-methyl-2-pyridone to methylpiperidol was attempted. Von Pechmann and Baltzer[2] found that the action of sodium amalgam on 1-ethyl-2-pyridone ruptures the ring, giving ethylamine. Ruzicka[16] reduced methylpyridone to methylpiperidone in neutral aqueous solution, in the presence of platinum black. Hydrogenation was tried in aqueous hydrochloric acid, using platinum black prepared from the oxide, but the same compound was obtained; only four atoms per molecule were absorbed.

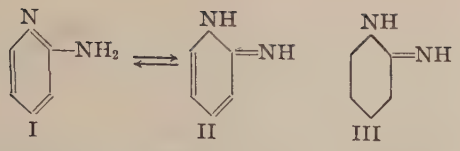
In the course of the identification of piperidine and of 2-piperidone, it was found that the corrected melting points of piperidine hydrochloride, piperidine picrate, and of 1-benzoyl-2-piperidone are, respectively, 244.5°, 150.5° and 120°, instead of 237°, 145° and 112°, as given in the literature. Piperidine hydrochloride was obtained by hydrogenating pyridine boiling constantly at 115°, and was purified by crystallization from absolute alcohol. The benzoyl piperidone was purified by sublimation on a steam-bath. Calibrated Anschütz thermometers were used in taking the melting points, the stems being totally immersed in glycerol.

Discussion of Results

The results outlined above show the marked influence of the nitrogen atom on the carbon atoms adjacent to it in the pyridine ring, a fact which has been brought out by many authors.[17] A consideration of the results of the hydrogenation of 1-methyl-2-pyridone leads to the conclusion that it behaves as a true dihydropyridine derivative, namely, 1-methyl-2-keto-dihydropyridine (1,2). The correctness of this view of its structure was indicated by the experiments of Decker and Engler[18] on 1,2- and 1,6-methylquinolone, and was demonstrated beyond reasonable doubt by the absorption spectrum measurements of Baker and Baly.[19] The fact that the compound combines catalytically with only four atoms of hydrogen affords fairly conclusive proof of its structure; it must be a true dihydropyridine derivative.

Aminopyridine, too, behaves as a dihydropyridine derivative on hydrogenation, since it takes up only four atoms per molecule. The explanation of this is afforded by the work of Chichibabin,[20] who showed that aminopyridine exhibits tautomerism,

[16] Ruzicka, *Helvetica Chim. Acta*, **4**, 472 (1921).
[17] Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).
[18] Decker and Engler, *Ber.*, **36**, 1171 (1903).
[19] Baker and Baly, *J. Chem. Soc.*, **91**, 1122 (1907).
[20] Chichibabin, *Ber.*, **54**, 814 (1921).



just as von Pechmann and Baltzer proved to be the case with 2-pyridone. He further showed that the imido tautomer (II) is the predominating one; and that this is to be considered a true dihydropyridine derivative is proved by the fact that only four atoms of hydrogen are absorbed catalytically. Tautomer I does, of course, exist, for it is the only form which could react with nitrous acid, Chichibabin having shown that the 1-methyl derivative of II is indifferent to this reagent. *In an acid solution* of the hydrogenated derivative, however, it must be concluded that there is no tautomerism, since the compound does not react with nitrous acid; its properties are evidently best expressed by the Structure III, which represents it as a derivative not of tetrahydro- but of hexahydropyridine, namely, 2-imidopiperidine. In the free state, however, this base must exist to a slight extent in the tautomeric amino form, for this is the only form which could give the Rimini reaction. Further evidence in support of Structure III is found in the hydrolysis to 2-piperidone, just as the "N-methyl-α-pyridone imide"[21] of Chichibabin undergoes hydrolysis to 1-methyl-2-pyridone. It is noteworthy that aminopyridine, in order to undergo hydrolysis, has to be "locked" in the form II by a methyl group on the ring nitrogen, while its tetrahydro derivative (III) does not. It is to be anticipated, on the other hand, that if locked in the *amino* form (I), as it is in dimethyl-aminopyridine, it would take up six atoms of hydrogen, just as 2-pyridone locked in the hydroxy form (as it is in methoxypyridine) takes up six. It is to be noted, however, that the indifference of 2-imidopiperidine to nitrous acid is anomalous, no matter what structure be assigned to it. Formula III explains the non-formation of 2-hydroxy-tetrahydropyridine, but it does not make apparent the reason for the failure to give a 1-nitroso derivative analogous to nitrosopiperidine.

The result of the hydrogenation of chloropyridine is in agreement with the well-known high reactivity of the chlorine in the 2 position, contrasted with that in the 3 position. The ease with which methoxypiperidine is split is, however, surprising, in view of the stability of methoxypyridine.

Platinum black prepared from the oxide was found to possess the advantages over the colloidal form reported by Adams and Voorhees.[14] The speed of hydrogenation of pyridine derivatives is far less than that of the nitrogen-free compounds tested by these authors, but it is noteworthy that the efficiency of 1 g. of platinum black was unimpaired after it had been used in the hydrogenation of over a dozen samples of the pyridine derivatives in amounts varying from 2 to 40 g.

[21] Better designated, "1-Methyl-2-imido-dihydropyridine (1,2)."

With regard to the more complete hydrogenation of aminopyridine effected by platinum oxide than by platinum black, it is probable that the oxide obtained by decomposition of the nitrate has the power of forming complexes different from those formed by oxygenated platinum black, at least with 2-aminopyridine and 2-imidopiperidine. Generalization further than this is impossible without data on the behavior of several mono- and diamines with platinum oxide. The extreme slowness of the hydrogenation is referable both to the base and to the platinum oxide, for the combinations *pyridine-platinum oxide* and *aminopyridine-platinum black* fix hydrogen more rapidly than *aminopyridine-platinum oxide* or *2-imidopiperidine-platinum oxide*. It is therefore logical to conclude that the latter two complexes are more stable than the former. Further evidence in favor of this view is the incompleteness of the reduction of the oxide in the presence of aminopyridine. Apparently the reduction of the oxide in the complex *aminopyridine-platinum oxide* is so difficult that the reduction of the aminopyridine proceeds simultaneously, and a small amount of the original oxide remains even after the ring has been completely hydrogenated.

It is probably the difficulty of the reduction of the oxide in the complex 2-imidopiperidine-platinum oxide that makes possible the hydrogenation of the base to ammonia and piperidine. Fixation of hydrogen at the C=N linkage must take place approximately as readily as the reduction of the oxide in the complex. Platinum oxide, then, exhibits in this particular case an unusual catalytic power which, despite its extreme slowness, may find useful application to other compounds.

Experimental Part

A C. P. grade of pyridine was dried over phosphoric oxide for several days and distilled; the fraction boiling at 114–116° was taken for the syntheses.

Apparatus for Catalytic Hydrogenation, and the Preparation of Platinum Black.—The apparatus used for the catalytic hydrogenations has no advantage over that of Lochte, Noyes and Bailey.[22] The hydrogenating bottle had a capacity of 800 cc., and 250 cc. of solution was always used. The calibration of the manometer was checked by hydrogenating 1.089 g. of pyridine in the presence of platinum black, that being the quantity required to absorb exactly one liter of hydrogen, measured at 22°, and 760 mm.

The platinum black was prepared by shaking platinum oxide, suspended in dil. hydrochloric acid containing 1 g. of pyridine, with hydrogen under pressure. When no further absorption took place, the shaking bottle was disconnected, and the platinum filtered off. It was kept ready for use on the moist filter.

[22] Lochte, Noyes and Bailey, *J. Am. Chem. Soc.*, **43**, 2601 (1921).

Preparation of 2-Methoxypyridine.—Methoxypyridine was prepared in three steps.

1. Pyridine was converted into 1-methyl-2-pyridone by O. Fischer and Chur's improvement[23] of the electrolytic oxidation method of Fischer and Neundlinger.[24]

2. Methyl pyridone was converted into 2-chloropyridine by the method of O. Fischer[5a] as improved by Fargher and Furness. It was found to be so slightly soluble in water, that in the steam distillation of 180g. quantities, it was separated and dried over potassium hydroxide, the water layer being discarded. Two distillations through a 40cm. column sufficed to free it from the dichloropyridine simultaneously formed; pure monochloropyridine, b. p., 171–171.5°, was obtained. It has a pungent, quinoline-like odor.

3. Chloropyridine was converted into methoxypyridine by boiling with sodium methoxide in methyl alcohol. Four equivalents of the reagent to one of chloropyridine were found to be necessary for a complete reaction. A concentrated solution of sodium methoxide was prepared by dissolving 8 g. of sodium in 72 cc. of absolute methyl alcohol, and after cooling, 10 g. of chloropyridine was added. The chloropyridine dissolved on shaking, but did not react until the solution was boiled. Refluxing was continued for six hours; the sodium chloride was then filtered off, washed with alcohol and dried. Five g. was obtained, the calculated quantity being 5.2 g. An excess of hydrochloric acid was added to the reaction mixture, and most of the alcohol distilled through a long column. The base was set free by sodium hydroxide, and steam-distilled. After evaporation of the dried ether extract, the base distilled at 142–143°. Pure methoxypyridine, b. p., 142.4° (760 mm.), d_4^{25} 1.041, d_4^0 1.064, has a pungent, unpleasant odor, but is not nauseating like pyridine.

Analysis. (Zeisel) Calc. for C_6H_7ON: OCH_3, 28.4. Found: 28.0.

Hydrogenation of 2-Methoxypyridine

a. With Sodium and Ethyl Alcohol.—Ladenburg's procedure for pyridine[7] was followed, using 5 g. of methoxypyridine and 15 g. of sodium. The resulting hydrochloride, after recrystallization from absolute alcohol, melted at 242–243°, and this point was not lowered by mixture with known piperidine hydrochloride. A sample of 0.5 g. was boiled for half an hour in the Zeisel apparatus, but the evolved vapors caused no precipitate in the alcoholic silver nitrate solution.

b. Electrolytic Reduction in Sulfuric Acid Solution with Lead Electrodes.—This was carried out according to the excellent directions of Tafel.[8] Five g. of methoxypyridine was dissolved in 100 cc. of 20% sulfuric acid, which served as the catholyte. This solution was electrolyzed until a sudden increase in the rate of hydrogen evolution took place. The current efficiency was about 47%. The solution was removed from the cell, treated with alkali and steam distilled. The hydrochloride of the base on recrystallization from absolute alcohol melted at 242–244°. Again the Zeisel test for methoxyl was negative.

c. Catalytic Reduction in 40% Acetic Acid Solution, Using Colloidal Platinum.—The catalyst was prepared by Skita's "inoculation" method. The solution as finally made up contained 0.6 g. of chloroplatinic acid, 0.3 g. of gum acacia, 5 g. of methoxypyridine, 50 cc. of glacial acetic acid and 70 cc. of water. This was shaken with hydrogen until no more was absorbed; the rate of absorption was slightly less than 1 cc. per minute. Piperidine hydrochloride was again identified as the reduction product.

d. Catalytic Reduction in Aqueous Hydrochloric Acid, Using Platinum Black.

[23] O. Fischer and Chur, *J. prakt. Chem.*, [2] **63**, 363 (1916).

[24] O. Fischer and Neundlinger, *Ber.*, **46**, 2544 (1913).

Proof that the First Stage in the Hydrogenation of Methoxypyridine is the Hydrogenation of the Ring.—In this and all succeeding hydrogenations, the volume of hydrogen was regulated. That required for 1 g. of methoxypyridine (6 atoms per molecule) was 665.5 cc. at 22° and 760 mm.; 1.503 g. therefore requires 1000 cc.

A solution containing 20 g. methoxypyridine and a slight excess of hydrochloric acid in 250 cc. was shaken with hydrogen until 13 liters, the quantity theoretically required for reduction to methoxypiperidine, had been absorbed. During filtration, the odor of methoxypyridine was apparent; the filtrate was made just alkaline to methyl orange, and the unchanged methoxypyridine distilled with steam. Approximately 4 g. separated from the distillate. The secondary base was freed by a slight excess of sodium hydroxide and steam-distilled into hydrochloric acid. The purified salt again proved to be piperidine hydrochloride.

Hydrogenation in Methyl Alcohol

Dry hydrogen chloride was passed into 200 cc. of absolute methyl alcohol until the increase in weight was 12 g.; 14.9 g. of methoxypyridine was added and the volume made up to 250 cc. with absolute methyl alcohol. Hydrogenation was continued until 9.92 liters, the volume required for 6 atoms per molecule, had been absorbed; the initial rate of absorption was 13 cc. per minute; the final rate was 8 cc. per minute. After the third and fourth crystallizations the resulting hydrochloride melted constantly at 244.5–246.0° (by a calibrated Anschütz thermometer). This point was not changed by mixture with known piperidine hydrochloride.

Analyses.[25] Calc. for $C_5H_{11}N.HCl$: C, 49.36; H, 9.95; N, 11.52. Found: C, 49.50; H, 10.20; N, 11.24.

The picrate, purified by crystallization from dilute alcohol, melted at 150.5–151.5° (corr.), and this point was unchanged by mixture with known piperidine picrate.

Analyses. Calc. for $C_{11}H_{14}N_4O_7$: C, 42.02; H, 4.49; N, 17.83. Found: C, 42.22; H, 4.60; N, 17.42.

The chloroplatinate, crystallized from dil. alcohol, melted at 198–199°, with decomposition.

Analysis. Calc. for $(C_5H_{11}N)_2.H_2PtCl_6$: Pt, 33.65. Found: 33.48.

Hydrogenation of 2-Methoxy-methyl-pyridinium-sulfate

Equivalent quantities of methoxypyridine (9.7 g.) and dimethyl-sulfate (5.6 g.), were warmed to 70–80° for two hours and the mixture was allowed to stand overnight. Hydrogenation of the quaternary salt was carried out in 250 cc. of absolute methyl alcohol in the presence of 1 g. of platinum black. The initial rate of absorption was 40 cc. per minute, and the final rate was 20 cc. Shaking was stopped after 6.4 liters (6 atoms per molecule) had been absorbed. The filtrate was evaporated to 50 cc., treated with an excess of sodium nitrite in the cold, and extracted four times with ether to remove any secondary base present. After the addition of alkali and steam distillation into hydrochloric acid, the chloroplatinate was prepared and recrystallized from 70–80% alcohol; it was almost insoluble in absolute alcohol; m. p., 209–210°.

Analyses. Calc. for $(C_6H_{13}N)_2.H_2PtCl_6$: Pt 32.09. Found: 32.02, 31.95.

[25] All analyses for nitrogen in compounds containing nitro groups were made by the Kjeldahl-Gunning-Jodlbauer-Arnold method; in compounds without nitro groups, by the Kjeldahl-Gunning-Arnold method. See Dyer, *J. Chem. Soc.*, **67**, 811 (1895). See also *Bur. Mines Tech. Paper*, No. **160** (1917), "The Determination of Nitrogen in Explosives," by W. C. Cope and G. B. Taylor.

Hydrogenation of 2-Chloropyridine

Dry hydrogen chloride was passed into absolute alcohol at 0° until the increase in weight was 40 g. per 100 g. of alcohol, and 6 g. of chloropyridine was dissolved in 250 cc. of this solution. The mixture was shaken with hydrogen at 3.75 atmospheres' pressure until 3.84 liters (6 atoms per molecule) had been absorbed. The rate of absorption was 13 cc. per minute. The residue obtained by evaporation of the solution was crystallized four times from alcohol; the products from the third and fourth crystallizations melted at 243–244°, and this point was not lowered by mixing the new substance with known piperidine hydrochloride.

The mother liquor from the first crop of crystals was treated with alkali, whereupon the powerful and unmistakable odor of pyridine, almost free from that of piperidine, was at once obtained.

Preparation and Hydrogenation of 2-Aminopyridine

Aminopyridine was prepared by the method of Chichibabin and Zeide[26] and was purified by two vacuum distillations; b. p., 81–82° (4 mm.). The product was pale yellow, and melted sharply at 58°.

In Dilute Hydrochloric Acid, with Colloidal Platinum.—To a solution of aminopyridine containing three equivalents of hydrogen chloride was added colloidal platinum prepared from 1.5 g. of chloroplatinic acid in the presence of 0.15 g. of gum acacia. The volume was made up to 100 cc., and the solution shaken with hydrogen at 3.75 atmospheres' pressure. The initial rate of absorption was 10 cc. per minute; after six hours it was 3 cc. per minute, and the catalyst was then shaken with air. Absorption thereupon took place at the initial rate, and ceased after two more hours. The treatment with air was repeated, but no more hydrogen could be introduced, although shaking was continued for half an hour. The total hydrogen absorbed was 4.60 liters, while that calculated for 4 atoms per molecule, at 22°, and 760 mm. was 4.58 liters. The platinum was precipitated with concd. hydrochloric acid. Evaporation of the filtrate under diminished pressure was necessary to avoid decomposition. The hydrochloride, after two crystallizations from absolute alcohol, melted at 157–158° (corr.).

Analyses. Calc. for $C_5H_{10}N_2.HCl$: C, 44.58; H, 8.24; N, 20.82. Found: C, 44.69; H, 8.43; N, 20.37, 20.86.

In Dilute Hydrochloric Acid, with Platinum Black.—A solution of 40.3 g. of 2-aminopyridine and two equivalents of hydrogen chloride in 250 cc., with 1 g. of platinum in suspension, was shaken with hydrogen at 3.75 atmospheres' pressure. Absorption took place at the rate of 50 cc. per minute, and ceased abruptly when 20.4 liters had been absorbed. The calculated amount for four atoms per molecule is 20.6 liters. From the recrystallized hydrochloride of 2-imidopiperidine thus obtained were prepared the chloroplatinate and picrate. The former was obtained as needles from 60% alcohol, with the characteristic orange color; m. p., after drying at 70°, 186.5–187.5° (corr.), with decomposition.

Analyses. Calc. for $(C_5H_{10}N_2)_2.H_2PtCl_6$: Pt, 32.10. Found: 32.26, 32.19.

The picrate was almost insoluble in absolute alcohol, hot or cold. It is most conveniently crystallized from hot 40–60% alcohol, and may be washed with cold 95% alcohol without loss. After two crystallizations, it melted at 209–210° (corr.).

Analyses. Calc. for $C_{11}H_{13}N_5O_7$: C, 40.85; H, 4.05; N, 21.67. Found: C, 40.73; H, 4.21; N, 21.21.

[26] Chichibabin and Zeide, *J. Russ. Phys.-Chem. Soc.*, **46,** 1224 (1914). Translation through the courtesy of the Research Information Service, The National Research Council.

The presence of the tautomeric 2-amino-tetrahydropyridine when the base is in the free state was indicated by a positive Rimini reaction. A solution of 1 g. of the hydrochloride in 50 cc. of water was decomposed with silver oxide and filtered. To 5 cc. of this solution were added 1 cc. of pure acetone and 1 drop of 1% sodium nitroprusside solution. A clear violet-red color was developed within ten seconds after mixing. This color was given neither by piperidine nor by ammonia.

The action of nitrous acid in the cold was tried, using the proportions of reagents recommended by Knorr[27] for piperidine, but the only substance isolated from the reaction mixture was unchanged 2-imidopiperidine hydrochloride, melting at 156–157°. The same result was obtained when the sodium nitrite was added to the acid solution at the boiling point.

Hydrolysis of 2-Imidopiperidine

On attempting to prepare the free base by decomposing the hydrochloride with potassium hydroxide, hydrolysis took place with the formation of ammonia and 2-piperidone. To ascertain the order of stability of the base, 10 g. of the hydrochloride was dissolved in 150 cc. of water, an excess of thoroughly washed silver oxide added, and a stream of nitrogen bubbled through the solution for 12 hours. The issuing gas was passed through hydrochloric acid, which was evaporated at the end of the run, but less than 5 mg. of solid residue was obtained. The silver chloride was filtered off, and the experiment repeated with the solution of the free base at the boiling point. After three hours, the hydrochloric acid trap gave on evaporation a residue of 3.55 g., which was shown to consist of ammonium chloride by analysis of its chloroplatinate.

Analysis. Calc. for $(NH_3)_2.H_2PtCl_6$: Pt, 43.96. Found: 44.11.

The other product of hydrolysis was identified as 2-piperidone by conversion into its benzoyl derivative. This was purified by sublimation on the steam-bath; m. p., 120–121°, corr.; Schotten[28] gives 112°.

Analyses. Calc. for $C_{12}H_{13}NO_2$: C, 70.90; H, 6.45; N, 6.90. Found: C, 70.82; H, 6.60; N, 6.54.

Hydrogenation in Neutral Aqueous Solution with Platinum Oxide

A solution of 4 g. of 2-aminopyridine hydrochloride in 250 cc. of water, with 1.256 g. of platinum oxide in suspension, was shaken with hydrogen until no more was absorbed. The initial rate of absorption was 32 cc. per minute; the final rate, 8 cc.; the total volume absorbed was 3.20 liters, while the total volume calculated was 3.32 liters (8 atoms per molecule, 3.07 liters plus 0.25 liter for 1.256 g. of $PtO_2.H_2O$). During filtration, the odor of ammonia was quite distinct, which was to be expected, since piperidine is a stronger base than ammonia, and only one equivalent of hydrogen chloride was present. A slight excess of hydrochloric acid was added to the filtrate, and a portion of it treated with chloroplatinic acid. Ammonium chloroplatinate was precipitated.

Analysis. Calc.: Pt, 43.96. Found: 43.72.

The remainder of the filtrate was evaporated under diminished pressure, and the alcohol-soluble portion crystallized from alcohol and ether; m. p., 242–243°; this was not lowered by mixing with known piperidine hydrochloride.

Attempt to Hydrogenate 2-Imidopiperidine with Platinum Black

A neutral aqueous solution of 5 g. of 2-imidopiperidine hydrochloride with 1 g. of platinum black in suspension was shaken with hydrogen for one hour, but no absorption

[27] Knorr, *Ann.*, **221**, 298 (1883).

[28] Schotten, *Ber.*, **21**, 2241 (1888).

took place. After shaking with air, the shaking with hydrogen was repeated, but again the result was negative.

Attempt to Hydrogenate 2-Imidopiperidine to 2-Aminopiperidine Using Platinum Oxide

A neutral aqueous solution of 7.85 g. of 2-imidopiperidine hydrochloride with 1.256 g. of platinum oxide in suspension was shaken with hydrogen until 1.2 liters had been absorbed. Without considering the unknown quantity used up in the *partial* reduction of the platinum oxide, 1.4 liters was required for 2 atoms per molecule. The odor of ammonia was again obtained during filtration. Separation of the bases was effected by conversion into the picrates. The first four crops from the hot aqueous solution proved to consist of 2-imidopiperidine picrate, melting at 207°; the fifth crop, after two crystallizations, melted at 151–152°. This point was not changed by mixing the material with known piperidine picrate. If 2-aminopiperidine had been formed in this experiment, no ammonia or piperidine should have been obtained, and only 15% of the 2-imidopiperidine should have been unchanged.

Catalytic Hydrogenation of 1-Methyl-2-pyridone

This was carried out in hydrochloric acid solution, using 23.3 g. of methyl pyridone and 0.5 g. of platinum black. The rate of absorption was 35 cc. per minute; the total volume absorbed was 10.37 liters. The calculated amount for 4 atoms per molecule was 10.34 liters. The product boiled at 103–104° (14 mm.): this agrees with the boiling point given by Ruzicka[18] for 1-methyl-2-piperidone.

Summary

1. A study has been made of the hydrogenation of 2-chloro-, 2-amino-, and of 2-methoxypyridine.

The molecule of chloropyridine adds two atoms of hydrogen, forming pyridine and hydrogen chloride, before the ring is attacked.

Aminopyridine adds four atoms per molecule, in the presence of platinum black, but it can be made to absorb eight atoms by the use of platinum oxide, yielding piperidine and ammonia.

One molecule of methoxypyridine apparently absorbs eight atoms of hydrogen before a second molecule is attacked; no base other than piperidine has been detected in the reduction product. Methylation of the nitrogen prior to reduction has no stabilizing influence on the molecule of methoxypiperidine.

2. 1-Methyl-2-pyridone and 2-aminopyridine behave, on reduction, as dihydropyridine derivatives.

3. Platinum oxide exhibits greater activity than platinum black in the hydrogenation of 2-aminopyridine.

4. The melting points of piperidine hydrochloride, piperidine picrate, and of 1-benzoyl-2-piperidone have been corrected, the figures being, respectively, 244.5°, 150.5° and 120°.

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BIOGRAPHY

The author of this dissertation was born in Richmond, Indiana, August 29, 1898. He received his preparatory education at the Friends School, Baltimore, where he graduated in 1915. During the years 1915–'18, he was a student at Oberlin College. From October, 1918, to January, 1919, he was a private in the Chemical Warfare Service of the U. S. Army, and was stationed at the Johns Hopkins Chemical Laboratory. In January, 1919, he was enrolled as a student in this University, and received the degree of A.B. the following June. Since October, 1919, he has been a graduate student in this University, with Chemistry for the principal subject, and Physical Chemistry and Pharmacology as subordinate subjects. He was awarded a University Scholarship for the year 1919–'20, and Hopkins Scholarships in 1920–'21 and 1921–'22. He was appointed Du Pont de Nemours Fellow for the year 1922–'23.